REMARKS

Specification Amendments

At page 5, line 26 through page 6, line 25, the paragraphs are amended to delete superfluous references to claim 1.

At pages 19-22 in the specification, Applicants have amended the names of certain compounds to correct an obvious typographical error. Specifically, in the named compounds containing thiophene rings, the "ethyl" bridge was inadvertently excluded. See, for example, Applicants' formula I which has an ethylene bridge between the piperazine ring and the R^1 group. See also the other named compounds listed in Applicants' specification. Applicants respectfully submit that the omission of the "ethyl" moiety is an obvious error with an obvious remedy in view of the rest of the application disclosure. See e.g., *In re Odu*, 170 U.S.P.Q. 268, 272 (CCPA 1971). See also *In re Nathan et al.*, 140 U.S.P.Q. 601 (CCPA 1964), *In re Sulkowski,* 180 U.S.P.Q. 146 (CCPA 1973), and *Spero v. Ringold*, 153 U.S.P.Q. 726 (CCPA 1967).

Claim Amendments

Claims 3, 4, and 8 are cancelled, and claims 1, 2, 5, 6 and 7 are amended to use language in accordance with conventional U.S. practice.

Claim 1 is also amended to recite that the acyl group has 1-6 C atoms and that Het^1 is a monocyclic heterocyclic ring system in which the hetero atoms are selected from nitrogen, oxygen and sulfur. Support for these amendments can be found throughout the specification. See, for example, page 7, lines 36-38 and page 9, lines 12-33. In addition, the proviso clause in claim 1 is amended to delete the second compound. See, for example, original claim 1 of the PCT application.

Claim 2 is amended to delete superfluous references to claim 1 and also to recite the option of a step for the formation of solvates. This step is inherent within Applicants' disclosure regarding solvates of the compounds of formula I.

As for, for example, claim 5, which recites both an eating disorder and bulimia,see,

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MPEP § 2173.05 (h) wherein it is stated that the group "amino, halogen, nitro, chloro and alkyl" is acceptable even though halogen is generic to chloro.

New claims 10-35 are directed to further aspects of the invention and are supported throughout the disclosure. See, for example, page 3, line 20-page 4 line 25; page 7, lines 36-38; page 9, lines 35-38; page 10, lines 1-11; page 10, line 16- page 12, line 7; and page 22, lines 4-9.

Rejections Under 35 U.S.C. §112, Second Paragraph and 35 U.S.C §101

Claims 1-8 are rejected as allegedly being indefinite under 35 U.S.C. § 112, second paragraph. In addition, claims 4, 5, 7 and 8 are rejected under 35 U.S.C. § 101 as being directed to non-statutory subject matter. These rejections are respectfully traversed. Contrary to the implication in the rejection, the term, "acyl" is a well known chemical term, one which is clearly understood by one of ordinary skill in the art. See, for example, the excerpt from Hawley's Condensed Chemical Dictionary, (14th Ed.) pg. 21 (2001), wherein acyl is defined as an organic acid group in which the OH of the carboxyl is replaced by another substituent. In any event, for purposes of furthering prosecution, claim 1 is amended above to recited that the acyl group has 1-6 C atoms. See, for example, page 7, line 36 of Applicants' specification.

The expressions "such as" and "for example" have been deleted from the claims. In addition, the second compound listed in the proviso of claim 1 has been deleted.

Claims 3, 4 and 8 have been deleted and claim 5 has been rewritten as a method claim. Subsection c of claim 2 clearly recites how radicals R^1, R^4 and/or R^5 are converted. One of ordinary skill in the art can readily recognize whether a given process embodiment falls within or outside the scope of Applicants' claim 2. Nothing more is required under the statute. Furthermore, it is a function of the specification, not the claims, to set forth operable proportions and similar process parameters. The claims are not rendered indefinite by the absence of such features. See, e.g., *ExParte Jackson et al*, 217 USPQ 805, 806 (POBA 1982). In addition, claim 2 is amended to further recite the optional step of formation of a solvate.

Claim 6 is amended above to recite a pharmaceutical composition comprising a compound according to claim 1 and a carrier. See, for example, page 16, lines 1-18. Moreover, the concepts of excipients, vehicles and other active compounds are readily understood by one or

ordinary skill in the art.

With regards to the rejection under 35 U.S.C. § 101, claims 4 and 8 have been canceled. In addition claims 5 and 76 have been rewritten as method claims.

In view of the above remarks, withdrawal of the rejection under35 U.S.C. § 112, second paragraph and the rejection under 35 U.S.C. § 101 is respectfully requested.

Rejection Under 35 U.S.C. §112, First Paragraph

Claims 1-8 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly not enabled. This rejection is respectfully traversed.

In the rejection, it is asserted that "generally not all solvents form solvates with all compounds." This assertion, however, in no way demonstrates any nonenablement associated with Applicants' claimed invention. Applicants' claims recite solvates, not solvates that cannot be formed.

Moreover, determination of whether a given solvent forms a solvate of a compound of Applicants' claim 1 clearly involves nothing more than routine experimentation. One of ordinary skill in the art need merely add the compound of claim 1 to the solvent in a manner which would permit one to observe whether dissolution occurred or not. The rejection presents no rationale as to why such experimentation to determine whether a solvate is formed constitutes undue experimentation.

The recitation of solvates in Applicants' claim 1 does not involve inoperative embodiments. Solvates which cannot be formed are not encompassed by the term solvates. Yet, it is noted that it is not a function of the claims to exclude all inoperative embodiments. See, for example, *Ex parte Janin* 209 USPQ 621763 (POBA 1979). In *Janin* the Examiner rejected claims on grounds that the group $-NR_3R_4$ read on unusual heterocyclic compounds including two compounds in which the nitrogen had a valence of 4. The Board reversed the Examiner's rejection noting that "such vague assumptions do not form a valid basis for the rejection."

With respect to the heterocyclic groups, the definition of Het^1 is relatively narrow and encompasses structurally similar compounds. Additionally, the number and types of heterocycles within Het^1 are finite. It would only involve routine experimentation for one of ordinary skill in

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the art to make, test and use the claimed invention to its full extent.

The courts have placed the burden upon the PTO to provide **evidence** shedding doubt on the disclosure as to whether the invention can be made and used as stated; see, e.g., *In re Marzocchi*, 439 F.2d 220, 169 USPQ 367 (CCPA 1971). The disclosure must be taken as being in compliance with the enabling requirement of the first paragraph of § 112, unless there is reason to doubt the objective truth of the statement contained therein. See *In re Marzocchi*, supra. No such evidence for doubting Applicants' disclosure is provided in the rejection.

Synthesis of the compounds of the claimed invention containing the group Het^1 requires no more than routine experimentation for one of ordinary skill in the art. Moreover, more than sufficient guidance is presented in the specification. See, e.g., page 5, line 26 – page 6, line 31, page 12, line 9 – page 14, line 24, and the examples on pages 18-23. With respect to the allegation that receptor binding is known to be generally structure-sensitive, the Office Action does not provide any reasoning as to why the heterocycles of Het^1 would not work for the intended indications.

As for the assertion regarding testing, the law does not require an applicant to test a compound in examples. See, for example, *Marzocchi*, supra, stating that whether "an enabling teaching is set forth, either by use of illustrative examples or by broad terminology, is of no importance." The MPEP also agrees by stating that "compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, does not turn on whether an example is disclosed." See MPEP § 2164.02.

The specification states that the claimed "compounds have a strong affinity for 5-HT_{2A} receptors; they furthermore exhibit 5-HT_{2A} receptor-antagonistic properties." See specification page 2, lines 10-12. The disclosed activity provides adequate basis for an enabling disclosure unless reasons are provided to doubt the objective truth of the disclosure.

Additionally, "the [enablement] requirement is satisfied if, given what they [, those or ordinary skill in the art,] already know, the specification teaches those in the art enough that they can make and use the invention without 'undue experimentation.'" See *Amgen v Hoechst Marion Roussel*, 65 USPQ2d 1385 (CA FC 2003).

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Further, applicants provide adequate teaching in the specification by which one of ordinary skill in the art can, without undue experimentation, test each of the compounds of the claimed species for activity. See, e.g., page 2, line 12 - page 3, line 8. Thus, any one of the claimed compounds can be made and tested by routine protocols known to those of ordinary skill in the art. As stated by the court in *Wands*, 8 USPQ 2d 1400 (1988), a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.

Additionally, the rejection appears to be a mixed rejection directed to enablement as well as to usefulness. However, only a section 112, first paragraph, rejection is issued without the corresponding section 101 rejection whereby the burden to rebut imposed on an applicant is higher than if the two rejections were imposed together. The MPEP states that "only where the totality of the record continues to show that the asserted utility is not specific, substantial, and credible should a rejection based on lack of utility be maintained. If the applicant satisfactorily rebuts a *prima facie* rejection based on lack of utility under 35 U.S.C. 101, withdraw the 35 U.S.C. 101 rejection and the corresponding rejection imposed under 35 U.S.C. 112, first paragraph." See MPEP § 2107. Based on this lower burden actually applicable in this case, reconsideration of the rejection is even more proper.

The Office Action also alleged that in case the non-statutory use claims are amended to method claims, the recited indications would not be enabled. Applicants respectfully disagree.

With respect to pharmaceutical inventions, an applicant is not required to test the claimed compounds in their final use. The Federal Circuit in *In re Brana*, 51 F.3d 1560 (Fed. Cir. 1995), stated that

> usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful can be well before it is ready to be administered to humans. If the courts were to require Phase II testing in order to prove utility for pharmaceutical inventions, the associated costs would prevent many companies from obtaining patent protection on promising new inventions, thereby eliminating an incentive to pursue, through research and development, potential cures in many crucial areas.

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Doubt has been held reasonable where, for example, the invention has been characterized as "highly unusual," *In re Houghton*, 433 F.2d 820 (CCPA 1970), as "incredible," *In re Citron*, 325 F.2d 248, (CCPA 1963), or as "too speculative," *In re Eltgroth*, 419 F.2d 918 (CCPA 1970). Because compounds having similar activities are known in the art (see, for example, the specification disclosure on page 3, lines 10-18), the existence of a new class of compounds having the claimed activities is not objectively doubtable, i.e., not "highly unusual," "incredible," and/or "too speculative."

In the rejection, reference is made to the article by Robichaud et al. The Examiner argues that this article does not acknowledge that 5-HT_{2A} antagonists can be used for treatment of the conditions recited in Applicants' claims. However, there is nothing in the rejection nor in the article by Robichaud et al. which indicates that its discussion on 5-HT_{2A} ligands is completely comprehensive. The article does acknowledge that the 5-HT_{2A} receptor has been implicated in the treatment of schizophrenia and depression.

The rejection also refers to the disclosure in Robichaud et al. of disappointing article Phase III clinical trials for a particular antagonist. However, the results for one compound outside the claims do not render Applicants' claimed invention non-enabled. Moreover, enablement under 35 U.S.C. § 112, first paragraph, in no way requires FDA approval or successful completion of Phase III clinical trials.

Applicants also submit herewith several references that further demonstrate the relationship between 5-HT_{2A} antagonist activity and a variety of indications. For example, see, "5-HT2A receptor gene polymorphisms in anorexia nervosa and bulimia nervosa" by Nacmias et al., linking 5-HT_{2A} antagonist activity and eating disorders; "Nefazodone in the treatment of premenstrual syndrome: a preliminary study" by Freeman et al, linking serotonin type 2 antagonism with improvements in premenstrual symptoms; "Effect of Pharmacologic Treatments on the Sleep of Depressed Patients" by Sharpley et al., linking 5-HT2A/2C receptor antagonist properties with increased slow-wave sleep and with sleep continuity; "5-HT2A promoter polymorphism in anorexia nervosa" by Sorbi et al., linking 5-HT2A and anorexia nervosa; "5-HT2A promoter polymorphism-1438G/A, anorexia nervosa, and obsessive-compulsive disorder" by Enoch et al., linking 5-HT2A with anorexia nervosa, obsessive-compulsive disorder, and with

anxiety;"5-HT1A agonists modulate mouse antipredator defensive behavior differently from the 5-HT2A antagonist pirenperone" by Griebel et al., linking 5-HT2A receptor antagonists and panic attacks and anxiety; "Activated astrocytes display increased 5-HT2a receptor expression in pathological states" by Wu et al., linking 5-HT2A receptors with cerebral infarction, hypertensive encephalopathy, Alzheimer's disease, Huntington's disease, frontotemporal dementia and Creutzfeldt-Jakob disease; "5-HT2A and 5-HT2C receptor polymorphisms and psychopathology in late onset Alzheimer's disease" by Holmes et al., linking 5-HT2A receptors with psychotic symptoms Alzheimer's disease; "Post-synaptic 5-HT1A and 5-HT2A receptors are increased in Parkinson's disease neocortex" by Chen et al., linking 5-HT2A receptors and Parkinson's disease and anti-depressant and anti-psychotic effects; and "A pharmacological analysis of serotonergic receptors: effects of their activation of blockade in learning" by Meneses et al., linking 5-HT2A with learning ability. The articles are summarized in the following chart:

Indication	Literature Citation
Neurological disorders	Wu, et. al.
Memory disorders	Meneses & Wong
Parkinson's disease	Chen, et. al.
Alzheimer's disease	Holmes, et. al., Wu, et. al.
Huntington's disease	Wu, et. al.
Eating disorders	Nacmias, et. al.
Panic attacks	Griebel, et. al.
Nervous anorexia	Enoch, et. al.
Sleep disorders	Sharpley & Cowen
Premenstrual syndrome	Freeman, et. al.
Cerebral infarction	Wu, et. al.
OCD	Enoch, et. al.

In view of the vast amount of work done in this area of research, linking claimed indications with the indicated activity of the claimed compounds, one of ordinary skill in the art

would not doubt the objective truth of the statements made in the specification. The mere absence of examples of specific disease treatment in the specification does not cause one of ordinary skill in the art to doubt the truth of the statements concerning the treatability of such diseases. The nature of the invention and the state of the prior art further demonstrate that Applicants' specification provides sufficient guidance to objectively enable one of ordinary skill in the art to make and use the claimed invention.

The Office Action also asserts that "there is no dosage regimen for such a range of uses for instant compounds." This assertion is also not a proper basis for an enablement rejection. Treatment regimens can be determined within the bounds of routine experimentation with respect to each claimed indication. Furthermore, the disclosure of treatment regimens or dosages in pharmaceutical patents is not required by the statutes, the courts, or the MPEP. In fact, the Federal Circuit held in *U.S. v. Telectronics*, 8 USPQ2d 1217 (1988), *cert. denied*, 490 U.S. 1046 (1989), that the cost and time needed to perform a dose response study did not establish that the amount of experimentation needed to be performed was undue.

In *Ex parte Skuballa*, 12 USPQ2d 1570 (1989), the Board addressed the enablement issue of a claim reciting diverse utilities, and stated that "We are satisfied that the skilled worker in this art could readily optimize effective dosages and administration regimens for each of the recited utilities. As is well known, the specific dosage for a given patient under specific conditions and for a specific disease will routinely vary, but determination of the optimum amount in each case can readily be accomplished by simple routine procedures."

The Federal Circuit in *Cross v. Iizuka*, 224 USPQ 739 (Fed. Cir. 1985), affirmed a USPTO Board of Patent Interferences decision addressing whether dosage levels need to be disclosed for a pharmaceutical in order to enable it. The Federal Circuit held that where sufficient credible evidence that one skilled in the art, without the exercise of inventive skill or undue experimentation, could determine dosage levels, disclosure of dosage levels is not necessary for enablement.

The MPEP also states that it is unnecessary to disclose dosages to satisfy the enablement requirement. See, *e.g.*, MPEP 2164.01(c): "it is not necessary to specify the dosage ... if it is known in the art that such information could be obtained without undue experimentation. If one skilled in the art, based on knowledge of compounds having similar physical or biological activity would be

able to discern an appropriate dosage ... without undue experimentation, this would be sufficient to satisfy 35 U.S.C. §112, first paragraph." Moreover, Applicants' specification provides guidance with regards to dosages. See, e.g., page 16, line 28-page 17, line 10.

Applicants' disclosure provides sufficient guidance to objective enable one of ordinary in the art to make and use the claimed invention. Withdrawal of the rejection under 35 U.S.C. § 112, first paragraph, is respectfully requested. Accordingly, an enablement rejection based on lack of disclosed dosages is not proper.

Claim Rejections Under 35 U.S.C §102(b)

Claims 1-8 stand rejected as allegedly being anticipated by U.S. Patent No. 5,032,604 (Baldwin et al.).

The rejection refers to the disclosure by Baldwin et al. (US '604) of the compound of example 17. This compound does not anticipate Applicants' claimed invention. Consequently, Applicants respectfully request that the rejection under 35 U.S.C. § 102(b) be withdrawn.

Claim Rejections Under 35 U.S.C §103

Claims 1-8 stand rejected as allegedly being unpatentable over U.S. Patent No. 5,032,598 (Balduss et al.). Applicants respectfully traverse this rejection.

Particularly, the rejection alleges that it would be obvious for one of skill in the art at the time of the invention to modify the compound depicted in example 24 by replacing the hydrogen atoms on the indole ring system with other groups. Applicants respectfully submit that the rejection provides no motivation for making these alleged modifications.

Baldwin et al. discloses a general formula of compounds at column 2. This general formula encompasses a vast number of different compounds. There is simply insufficient motivation for one of skill in the art to make the alleged modification to render Applicants' claimed invention unpatentable.

Baldwin et al. ('598) does not include indole compounds within their preferred group of compounds. See the listing of preferred Ar and B groups at Column 3, line 66 – Column 4, line 38. Moreover, Baldwin et al. disclose only three indole compounds, specifically the compounds

of Examples 24-26. None of these compounds exhibit a substituent in the indole ring, and nothing within the disclosure of Baldwin et al. would lead one to select an indole compound and then modify it in the manner suggested by the rejection.

Thus, Baldwin et al. provides no preferences or examples for making the alleged modification. Consequently, there are insufficient blazemarks or guideposts to teach or suggest Applicants' claimed invention.

In view of the above remarks, it is respectfully submitted that US '598 fails to provide sufficient motivation which would lead one of ordinary skill in the art to modify the compounds disclosed therein in such a manner as to arrive at a compound in accordance with Applicants' claimed invention. Withdrawal of the rejection under 35 U.S.C. § 103 is respectfully requested.

Claim Rejections Under Non-Statutory Double Patenting

Claims 1-8 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 1-8 of co-pending Application No. 10/031,566. Applicants respectfully submit that this rejection should be withdrawn because claims 1-8 of U.S. patent application No. 10/0351,566 do not teach or suggest compounds within Applicants' claims. Compare R^4 of Applicants' claims and the -CO-R^3 group of the claims of Serial No. '566, for example.

In view of the above remarks, full reconsideration is courteously requested. If there are any remaining issues, which can be expedited by a telephone conference, the Examiner is courteously invited to telephone counsel at the number indicated below.

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The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

Respectfully submitted,

Brion P. Heaney, Reg. No. 32,542
Attorney/Agent for Applicant(s)

MILLEN, WHITE, ZELANO
& BRANIGAN, P.C.
Arlington Courthouse Plaza 1, Suite 1400
2200 Clarendon Boulevard
Arlington, Virginia 22201
Telephone: (703) 243-6333
Facsimile: (703) 243-6410

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